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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/382,088	08/24/1999	ERNEST G. HOPE	HOPEP001	4793

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/382,088	HOPE ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51,60-68,74,75 and 293* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51,60-68,74,75 and 293* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 5/10/07 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks filed 5/10/07 have been entered.

2. Claims 51, 60-68, 74, 75, and 293 are under examination.

3. In view of the instant amendments, all previous rejections have been withdrawn. Remarks relevant to new rejections will be addressed.

4. The specification is objected to for the following informalities:

A) The disclosure is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code. See, for example, page 13 of the specification. Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable code. See MPEP 608.01.

5. Claim 65 is objected to as it is unclear how it differs from Claim 63.

6. The following are new grounds for rejection.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 62-65, 67, 74, and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) Regarding Claims 62-65, the recitation of percent homologies renders the claims broader than Claim 61 from which they depend.

B) Regarding Claims 67, 74, and 75, the recitation of percent homologies renders the claims broader than Claim 66 from

which they depend.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 51, 60-68, 74, 75, and 293 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification is not enabled for the claimed method employing peptides or polypeptides other than those consisting of SEQ ID NOS:3 and 6.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is

unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

In the submission of a specification Applicant has many choices. Applicant can either submit a thorough discussion of the claimed invention or Applicant can submit just a minimal description of the invention itself. In choosing to disclose as little as possible, Applicant does, however, face the possibility that the invention might be limited to only that which has been disclosed, i.e., Applicant has sacrificed possible breadth. In the instant case, Applicant has chosen to provide only a minimal disclosure. Applicant has chosen not to disclose the mechanism by which the claimed method might function and Applicant has further chosen not to disclose how the specific degenerate peptides employed in the specification were arrived at. While a vague mention of "shared homology" between huHSP47 and HLA-A2 is disclosed in Example 8, there is no disclosure of the relevance of said shared homology to the method of the instant claims. Regardless, it is noted that the protective effect of the claimed method is disclosed as being non-MHC restricted.

The only actual support for the claimed method offered in the instant specification is the part of Example 3 spanning pages 54 and 55. HuHSP47 (SEQ ID NO:6) and a fragment of the protein (SEQ ID NO:3) are shown to protect EC from CIK-mediated lysis. Note that the specification fails to even disclose how the fragment of SEQ ID NO:3 was arrived at. The specification does show, however, that some fragments of SEQ ID NO:6, e.g., fragments *comprising* SEQ ID NO:3, do *not* function in the claimed method (deletion mutant 2) presumably because of "altered conformation".

As set forth previously, the specification fails to provide guidance as to how to use a composition comprising any immunoprotecting variant or fragment of the polypeptide comprising the amino acid sequence of SEQ ID NO:6 or SEQ ID NO:3. Predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acids in the sequence, if any, are

tolerant of modification and which are conserved or less tolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its functional usefulness, as evidenced by the teachings of Abaza et al. (1992, of record). Abaza et al. teach that even a single amino acid difference in an antigen may effect antibody binding by teaching that an amino acid substitution of myoglobin outside the epitope recognized by a monoclonal antibody causes the myoglobin to be unreactive with said antibody. Therefore, predicting which polypeptides, fragments, variations and modifications of HSP47, would retain the desired immunoprotective characteristics and therefore will be useful in a method for reducing immune mediated damage is complex and well outside the realm of routine experimentation.

Accordingly, there is no way to determine which of the variant proteins and peptides encompassed for use in the method of the instant claims might function in an effective treatment and which might not.

Applicant's arguments, filed 5/10/07, have been fully considered but they are not persuasive. Applicant argues that little experimentation would be necessary and that it is known in the art how to make polypeptide sequence substitutions.

While the art may recognize how to make substituted polypeptide sequences, the art does not recognize how substituted polypeptides *that would function in the claimed method* would be made. At best, a method of trial and error might be employed. Given that said methods comprise no particular expectation of success with any particular test candidate, said methods are not enabled unless the test pool is limited. In the instant case, no guidance has been provided as to which amino acids might be substituted and which might not, thus all possibilities must be tested. Indeed, the claims would even encompass the use of variants of SEQ ID NO:6 in which the sequence of SEQ ID NO:3 had been completely eliminated by substitution. Given claims drawn to the use of SEQ ID NO:6 variants with as little as 80% identity, proteins comprising 1 to 80+ substitutions, additions, and/or deletions, each substitution, addition, and/or deletion comprising one of 20 possible amino acids, i.e., an essentially countless number of variants, are encompassed for use in the method of the instant claims. The testing of an essentially countless number of variants cannot be considered to be routine experimentation.

11. Claims 51, 60-68, 74, 75, and 293 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of a sequence *comprising* SEQ ID NO:6 or SEQ ID NO:3, or 80%, 90%, or 95% variants thereof, effective to prevent damage of cells, tissues, or organs by lymphocytes, NK cells, or NK-like cells. As set forth above, it is clear that the claims encompass the use of an essentially unlimited genus of variant proteins and peptides, none of which have been disclosed. As set forth in *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 and reiterated in University of *Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1892, "A description of what a material does, rather than what it is, usually does not suffice". In the instant case the proteins and peptides are described by function only, no meaningful structural characteristics are disclosed. Thus, an adequate written description of the claimed genus has not been disclosed. Accordingly, one of skill in the art would conclude that the specification fails to disclose either common functional *and* structural features, or a representative number of species, to describe the claimed genus of proteins and peptides encompassed for use in the method of the instant claims.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 51, 60-68, 74, 75, and 293 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hoppe et al. (1995, IDS).

Hoppe et al. teaches a method for reducing immune-mediated damage to cells, tissues or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of polypeptide comprising Hsp47 which comprises the amino acid sequence AVLSAEQLR (SEQ ID NO:3), or SEQ ID NO:6, which encompasses the claimed variants thereof and a sequence which hybridizes with a nucleic acid sequence of SEQ ID NO:4, wherein the immune-mediated damage is caused by CIK cells. The reference further teaches the purification of the protein and its use in reducing immune-mediated damage caused by lymphocytes (vascular leak syndrome) (see particularly the last line of the abstract).

Applicant's arguments, filed 65/10/07, have been fully considered but they are not persuasive. Applicant argues that the reference does not teach the administration of an isolated or recombinantly expressed polypeptide.

The reference teaches the purification of Hsp47. Said Hsp47 is thus, "isolated" before administration to a SCID/hu mouse. Applicant further appears to imply that the p46 of the reference is not be HSP47. If that is Applicant's argument, Applicant should state it clearly. Should Applicant make such a statement, Applicant is advised that a request for complete information under 37 CFR 1.105 regarding the protein of the reference will follow.

15. Claims 62-65, 67, 74, and 75 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the

relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) a polypeptide having at least 95% sequence identity to SEQ ID NO:6 (Claims 62 or 75).

B) a polypeptide having at least 90% sequence identity to SEQ ID NO:6 (Claims 63, 65, or 74).

C) a polypeptide having at least 80% sequence identity to SEQ ID NO:6" (Claims 64 or 67).

Applicant is advised that the specification discloses at page 10 polypeptides which have at least 70% identity, or greater than 90% or 95% identity, with SEQ ID NO:6.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

18. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see www.uspto.gov/ebc/newusers.html. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

7/4/07

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